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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/781,340	02/17/2004	Neil S. Cutshall	60117-106	9233

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EXAMINER	
DESAI, RITA J	

ART UNIT	PAPER NUMBER
1625	

NOTIFICATION DATE	DELIVERY MODE
07/09/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Office Action Summary	Application No.	Applicant(s)	
	10/781,340	CUTSHALL ET AL.	
	Examiner	Art Unit	
	Rita J. Desai	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) *1-30,43 and 44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-42, 45, 46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/9/08 has been entered.

Claims 1-46 are in the application.

Claims 1-30, 43-44 are withdrawn.

Claims under examination are 31-42, 45 and 46.

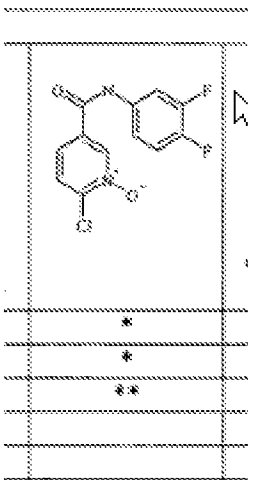
Applicants arguments are not found to be persuasive .

Applicants argue that example 5 has a heteroaryl R1 is an imidazol-l-yl example 7 wherein R1 is a pyrrolyl and example 15 has a Cl for the R4 which can be easily converted to any appropriate heteroaryl or N-heterocycle aliphatic ring under standard conditions to obtain the compounds of the inventions.

Applicants further argue that example 21 and 22 disclose a number of compounds that antagonize chemokine receptors.

The scope of the compounds are given in 2 sets. One in which R1 is always a Cl and NR2R3 varies and in the other set NR2R3 is fixed which is a fluoro phenyl and the R1 varies.

In table 7 some activity data with a * is given for 9 compounds. It does not say what



that * indicates. Some of these compounds are also not tested.

Applicants claims are not just drawn to inhibiting CCR5, CXCR1, CXCR2, NPY1 and Somatostatin, but to antagonizing all chemokine receptors, inhibiting a G-protein-coupled 7TM receptor and also as given in claim 36 to treating various diseases such as cancer graft vs host diseases.

36. (Original) The method of claim 32 for the treatment of a disorder selected from Inflammatory Bowel Disease (IBD), psoriasis, rheumatoid arthritis, Acute Respiratory Distress Syndrome (ARDS), cancer, atherosclerosis, reperfusion injury, and graft vs. host disease.

There are various types of cancers and applicants do not have any assays to indicate it can treat any of them.

The unpredictability of treating these various disorders coupled by the complex permutation and combinations of the variables in the compounds makes the art even more unpredictable.

There are also various types of chemokine receptors which act on the G –proteins.

According to Wikepedia there are several chemokine receptors and ligands. Each is found in a different location and are of different types.

Even if there was some activity at one of he receptors it does not mean or imply that it would behave in the same way at a different location.

The rejection still stands and is being repeated here.

The rejection of the claims under 35 U.S.C. 112 first paragraph scope of enablement still stands.

) The breadth of the claims: The instant claims encompass many compounds from an aromatic carbocyclic moiety to an aromatic carbocyclic moiety having many large electron withdrawing and bulky groups substituted on it to a moiety having many heterocyclic rings. These compounds cover a very wide range of compounds. With R1 and R4 being various heteroaryl, heteroalkyl, heterocyclic aliphatic ring.

2) The nature of the invention: The invention is a (highly) substituted compound that is useful to treat and inhibiting various receptors and to treat numerous diseases including cancer .

3) The state of the prior art: Applicants own background information on the Chemokine receptors and G-proteins indicate that they are of several types and are found in all the various cells and tissues and are of a variety of types. G-protein -coupled 7TM receptor would still be another type. The inhibiting of the various cellular events or treat the various diseases by these receptors is not an absolute predictability. The state of the prior art is that it involves screening in vitro and invivo to determine which compounds exhibit the desired pharmacological activities. There is no absolute predictability and no established correlation between in vitro activity and the treatment of various diseases and also the IC 50 values, as the in vitro data is not a reliable predictor of success even in view of the seemingly high level of skill in the art. The existence of these obstacles

establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

Please see article by James Cumming et al Expression and Function of Chemokine Receptors CXCR1 and CXCR2 in Sepsis. The article clearly illustrates the complication of selecting therapeutic targets to reduce inflammation. The study clearly shows the specificity of the receptor and the disease.

4) The level of one of ordinary skill: The ordinary artisan is highly skilled.

5) The level of predictability in the art: It is noted that the pharmaceutical art is unpredictable , requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F. 2d 833, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statue. The level of unpredictability is in the art is very high couples with the fact that applicants compounds of formula I has a very wide scope with all the various R1 and R4 groups. For e.g. the compounds which differ by a methyl group also show different properties, for e.g. theophylline and caffeine. One of them is a bronchodilator and they differ only by a methyl group.

6) The amount of direction provided by the inventor: The inventor provides very little direction in the instant specification. There are no examples with the R being hetero cyclic groups and also there is no data provided to show that these compounds do indeed treat various diseases. The only data provided is of 9 compounds that have an IC50 as given in **table 6** page 67, 68 of the specifications. Even this data is not consistent. The first compound does not show any CCR5 activity.! And the second last does not have any NPY1 and somat activity.!

7) The existence of working examples: The instant specification has only 9 examples with a few assays.

8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure: Since there are no working examples, and since the state of the art clearly indicates that diseases are related to very specific sub type receptors coupled with the fact that drugs have very limited predictability , the amount of experimentation is very high and burdensome and it not clear who the patient in need there of is who would require the antagonizing or inhibiting treatment since the scope of the claim is drawn to any chemokine receptor, inhibition of any chemokine mediated cellular "event" , without any indication of which patient population.

Taking the above eight factors into consideration, it is not seen where the instant specification enables the ordinary artisan to make and/or use the instantly claimed invention.

A small scope of compounds according to the invention have been made. The assay test is noted. While these screening test in an enzyme assay provides data in certain inhibiting activity, it does not provide sufficient operational guidance in an "individual" in patho-physiological environment.

Genetech Inc Vs Nova Nordisk 42 USPQ 2d 1001.

"A patent is not a hunting license. It is not a reward for search but compensation for its successful conclusion and patent protection is granted in return for an enabling disclosure of an invention , not for vague intimations of general ideas that may or may not be workable."

Applicants have provided several references to indicate that their compound do indeed treat any and all the various disorders.

1) applicants have provided only 9 compounds with few assays.

The scope of the compounds is unusually large. The only data provided is of 9 compounds that have an IC50 as given in **table 6** page 67, 68 of the specifications. Even this data is not consistent. The first compound does not show any CCR5 activity.! And the second last does not have any NPY1 and somat. activity.!

The art is highly unpredictable.

The references provided does not teach that by antagonizing chemokine, one would be able to treat effectively disorders such as cancer , IBD, reperfusion injury, graft vs. Host diseases.

Applicants claim reads "patient" " in need thereof" and "effective amount" implies that it is treating some diseases. The diseases listed in the specifications has a laundry list.

The specification are enabled for a limited scope of compounds, wherien R1 is a halogen or a SO2- alkyl , or So2- alkylaryl, and SO2-cycloalkyl and n=0.

Claims 41 reads " an inflammation "event". The scope of the event is also not enabled.

The claim 40 reads compounds " modulate" the binding of MIP-1Beta to a CCR5 cell receptor. As does claim 38 and 39. The claim is not enabled for the term Modulating the binding. Modulating means changing. Claim 31 states that it is antagonizing. Modulating would inherently mean that it would antagonize or agonize the receptor.

Applicants argue that changing a Cl to another heteroaryl group under standard conditions is routine .

This is incorrect.

In view of the preface by Dorwald in " Side Reactions in organic Synthesis " it is clear that synthesizing compounds is not just routine.

As stated in the preface to a recent treatise:

"Most non-chemists would probably be horrified if they wereto learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work .....Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious) ....." Dorwald F. A.

Side Reactions in Organic Synthesis, 2005, Wiley: VCH, Weinheim pg. IX of Preface.

There are also several case laws which support the unpredictability in chemical and biological art.

Ex parte DIAMOND, 123 USPQ 167 (Bd. Pat. App. & Int. 1959) where the examiner was affirmed for a scope of enablement rejection, and the court stated:

Scope of claims should not be unduly extensive in chemical fields where applicability is highly speculative or not explored; subject matter which relies upon prediction for its support is unpatentable.
Specification contains 23 specific examples, but they are to preparation of relatively simple compounds; this is relatively meager and non representative disclosure to support claims embracing millions of compounds.
Applicant may not preempt unduly large field by expedient of making broad prophetic statements in specification and claims unless accuracy of such statements is sufficiently supported by well established chemical principles or by sufficient number of examples.
"The term 'substituted' without modification or restriction includes all compounds wherein one or more of the atoms or radicals of the original compound have been replaced by one or more other atoms or radicals. Without any limitation on the character or number of substituents it becomes apparent that the quoted term may be considered inclusive of almost any possible substance and the claims under consideration are either of unlimited or indeterminate scope. We are of the opinion that the reasoning of the courts in Schering Corp. v. Gilbert, 68 USPQ 84, and Hercules Powder Co. v. Rohm & Haas, 70 USPQ 297, is controlling."
embrace millions of compounds. It should also be observed that appellant is working in a field where little prediction is possible and this Board has on several occasions held that the scope of claims should not be unduly extensive in fields where applicability is highly speculative or not explored and that subject matter which relies upon prediction for its support is unpatentable. Ex parte Middleton, 87 USPQ 57; Ex parte Kauck et al., 95 USPQ 197 , Ex parte Rosenkranz et al., Pat. No. 2,715,637.
In Minnesota Mining and Mfg. Co. et al. v. Carborundum Co. et al., 155 F.2d 746, 69 USPQ 288 , the court held that "An inventor cannot disclose a small number of components which will serve as a springboard for claiming an entire class."

In addition *In re Fouche* 169 USPQ 429 dealt with a similar issue with respect to how to use

requirement of 112 1st paragraph,

"Inclusion of representative examples is not required to enable a person skilled in the art to use a generic invention; nevertheless, applicant must use some technique of providing teaching of how to use which is commensurate with breadth of protection sought by claim, unless such knowledge is already available to persons skilled in the art; thus, where applicant undertakes to define invention by recitation of a Markush group, he must enable one skilled in the art to make and use at least one composition employing each member of group.
Both the examiner and the board noted that none of the working examples pertained to compounds wherein Z was heterocyclic. Appellant is quite correct in contending that, under our decisions in In re Robins, 57 CCPA 1321, 429 F.2d 452, 166 USPQ 552 (1970), the inclusion of

representative examples is not required to enable a person skilled in the art to use a generic invention. Nevertheless, an applicant must use *some* technique of providing teaching of how to use which is commensurate with the breadth of protection sought by the claim, unless such knowledge is already available to persons skilled in the art.
It seems clear, and it is not disputed by appellant, that where an applicant undertakes to define his invention by the recitation of a Markush group, he must enable one skilled in the art to make and use at least one composition employing each member of the Markush group. The examiner and the board did not believe that appellant had done so as to the heterocyclic members of the group. While they noted the absence of examples using heterocyclic moieties, we do not find that they viewed examples as mandatory. The issue before us is whether appellant has provided *any* teaching of how to use compounds containing the heterocyclic members of the Markush group. The only reference to heterocyclic radicals in the specification is the statement that "the invention provides" compounds of the structure shown in claim 1, wherein Z may be, among other possibilities,
a mononuclear, nitrogen-containing heterocycle connected to the chain A by the nitrogen atom, and optionally containing an oxygen, sulphur, or second nitrogen atom in the ring and optionally substituted by one of more alkyl radicals containing 1 to 5 carbon atoms each, such as 1-pyrrolidyl, piperidino, morpholino, 1-piperazinyl, or 4-alkyl-1-piperazinyl. "

See also: *Schering Corporation v. Gilbert et al.*, 68 USPQ 84 (2d Cir. 1946)
It was shown in evidence and by way of admissions elicited by the defendants from the plaintiff before trial that one skilled in the art of organic chemistry may start in the group of the acetic acid radical and the radicals of homologues of acetic acid to which the patent relates, for instance, with the simple hydrocarbon called methane and theoretically progress along the series in the general group called alkanes from one substance to another by increasing the size of the molecules in steps of one carbon atom and two hydrogen atoms. At least formulas for such substances, as well as for others, can be written in an indefinite chain. Also it was shown that for the hydrogen atoms of the alkane molecules the atoms of what are called halogens may be substituted and so may the atoms of other groups including the residue of the hydrocarbon benzene. The latter is represented in chemical formulas by a hexagon which is called the benzene ring and, as changes in the atomic structure of the molecule occur, the ones introduced take varying positions within the ring which positions determine the nature of the compound.
Theoretically a multitude of substances not as yet found in nature and not as yet compounded could be synthesized, if skilled organic chemists were given the time and materials with which to work, and actually the formulas for them could be written. There is, however, a practical limit upon synthesis, though the extent of that is not fully known, for some of the new theoretical compounds might be impossible to create, and some would be so unstable that they would disintegrate either at once or in short periods of varying length. Moreover, while analogy is at times useful, organic chemistry is essentially an experimental science and results are often uncertain, unpredictable and unexpected.

And *Nationwide Chemical Corporation, et al. v. Wright, et al.,* 192 USPQ 95 (M.D. Fla. 1976)

"with respect to generic claims to chemical and biological inventions, the scope of the claims is limited to what those skilled in the art could reasonably predict from the inventor's disclosure. This precept recognizes that one skilled in these chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances. Thus, in so-called "chemical" patent law practice, the claims of a patent are limited by the scope of what the disclosure reasonably teaches to one skilled in the art."

Conclusion

Claims 31-42, 45 and 46 are rejected.

Claims 1-30, 43-44 are withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rita J. Desai whose telephone number is 571-272-0684. The examiner can normally be reached on Monday - Friday, flex time..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Rita J. Desai
Primary Examiner
Art Unit 1625

R.D.
July 2, 2008

/Rita J. Desai/
Primary Examiner, Art Unit 1625